Alerts, Notices, and Case Reports

Allopurinol Hypersensitivity Syndrome Revisited

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ALLERGIC DRUG REACTIONS continue to be the leading cause of iatrogenic illness in adults.[1] Since the first case of allopurinol hypersensitivity was reported in 1970, more than 100 cases have subsequently been reported in the literature.[2] It is noteworthy how infrequent this reaction is in light of the 240 million doses that are prescribed annually.[3] Yet, although rare, this life-threatening reaction is often preventable if caution is exercised and dosages in patients with renal insufficiency are modified. We report a case of severe allopurinol hypersensitivity syndrome that manifested many features typical of sepsis along with advanced renal and hepatic dysfunction.

Report of a Case

The patient, a 42-year-old woman with hypertension, insulin-dependent diabetes mellitus, mild renal insufficiency, and gout, was admitted to the hospital for the evaluation of fevers, night sweats, rapidly progressive renal insufficiency, and a diffuse maculopapular rash. Ten days before admission, a rash developed predominantly on the patient's abdomen and lower extremities, and she was seen in the outpatient clinic. She was noted to be taking insulin, furosemide, captopril, nifedipine, colchicine, and allopurinol.

There was no history of antibiotic use. The patient's allopurinol therapy was discontinued at the time of her initial evaluation, and the rash faded. The rash recurred, however, along with fevers and night sweats two days before admission. On her admission to the medical intensive care unit, the patient appeared ill, had a temperature of 38.4°C (101°F), a pulse rate of 114 beats per minute, and a blood pressure of 110/40 mm of mercury. The findings of the examination were notable for erythroderma of the face, neck, and arms, along with an erythematous maculopapular rash of the abdomen and lower extremities. Her other physical findings were normal.

Initial laboratory tests revealed a leukocyte count of 15×10^9 per liter with 0.67 segmented neutrophils, 0.15 bands, 0.08 lymphocytes, and 0.06 eosinophils. Her blood urea nitrogen level was elevated at 40.0 mmol per liter (112 mg per dl); serum creatinine, 795.6 μmol per liter (9.0 mg per dl); aspartate aminotransferase (formerly SGOT), 115 IU per liter; and alanine aminotransferase (formerly SGPT), 446 IU per liter. A urinalysis was notable for moderate proteinuria, granular casts, and pyuria. A Hansel's stain for urinary eosinophils was negative. The most recent creatinine level before the onset of this illness was 380 μmol per liter (4.3 mg per dl).

Because of a concern regarding sepsis in the setting of her renal dysfunction and hypotension, pulmonary artery catheterization was done, revealing a cardiac output of 9.0 liters per minute, systemic vascular resistance of 400 dynes per second per cm, and a pulmonary capillary wedge pressure of 18 mm of mercury. Further evaluation included an echocardiogram that did not reveal vegetations and abdominal and pelvic computed tomographic scans that were normal.

The patient was treated with empiric broad-spectrum antibiotic therapy after specimens of blood, urine, and sputum were sent for culture. Consultations were obtained from the dermatology service as well as the critical care and infectious diseases services. Multiple skin biopsies were taken, and all of her ongoing medications, except for insulin, were discontinued.

On hospital day 3 the patient's skin was desquamating, she was persistently febrile, and her leukocyte count was 27×10^9 per liter with 0.15 eosinophils. Her aminotransferase values remained elevated, and she became progressively anuric. All cultures remained negative, however, as were viral serologic tests for hepatitis.

At this time, the results of her skin biopsies returned, and the specimens revealed a mild spongiotic epidermis with a dermis that contained lichenoid and superficial perivascular lymphohistiocytic infiltrates with eosinophils, consistent with a drug eruption. The diagnosis of an adverse reaction to allopurinol was entertained given her aforementioned history. Hemodialysis and a regimen of methylprednisolone sodium succinate, 125 mg intravenously every six hours, were begun, and the antibiotics were discontinued. The steroid doses were rapidly tapered over a five-day period. One day after beginning this treatment, the patient's fever defervesced, her eosinophilia resolved, and her sense of well-being markedly improved. An oxipurinol concentration measured 14 days after her last dose of allopurinol and after one hemodialysis session was elevated at 9.3 μmol per liter. Peak oxipurinol concentrations after a single 300-mg dose of allopurinol are about 5.0 μmol per liter (ARUP, Salt Lake City, Utah).

Ten days after admission the patient was discharged; she remained afebrile, her desquamation was resolving, and laboratory abnormalities were returning to normal, although she continued to require dialysis. Serologic

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tests for antinuclear antibody, human immunodeficiency virus, and hepatitis were all negative. Twelve days after discharge, the patient was noted to have recurrence of her erythematous maculopapular rash and had a leukocyte count of 16×10^9 per liter with 0.32 eosinophils, but she was otherwise asymptomatic without aminotransferase elevation while being dialyzed three times a week. At this point, glucocorticoid therapy was reinstituted and tapered over a two-week period. The eosinophilia resolved, and the maculopapular rash gradually faded without progression. The patient required continued hemodialysis for an additional two months but subsequently became stable with a serum creatinine level of 486 μmol per liter (5.5 mg per dl). Except for the allopurinol, all other medication regimens have since been reinstituted without further complications.

Discussion

The allopurinol hypersensitivity syndrome is defined by a clear history of allopurinol use; a clinical picture consisting of two of the following major criteria or one major and one minor criteria: major: rash (diffuse maculopapular or exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis), worsening renal function, or acute hepatic toxicity; minor: fever, eosinophilia, or leukocytosis; and a lack of exposure to another drug that may have caused a similar clinical picture.[4] The rash may change over time, with the most common pattern being a maculopapular pattern evolving into exfoliative dermatitis. If steroids are used, the rash might recur with tapering, as evidenced in this case.[5] The leukocytosis is often characterized not only by eosinophilia, but also by the presence of band forms without clear evidence of infection. Indeed, our patient had a substantial number of bands on her peripheral smear, and her clinical picture initially was highly suggestive of sepsis. Many patients have underlying chronic diseases, with renal insufficiency, hypertension, diabetes mellitus, and congestive heart failure being the most common. Consequently, these patients are typically on concomitant medication regimens, including diuretics. Some have speculated that the coadministration of thiazides, in particular, may predispose to the development of this syndrome.[6] This is presumably related to the thiazide diuretics inhibiting the excretion of oxipurinol, resulting in excessively high blood concentrations. Onset is typically two to six weeks after beginning treatment, but the range is large—1 to 728 days. Most patients are on a dosage of 300 mg per day, despite having underlying renal insufficiency. Overall mortality in the reported cases is about 25%.

The likely mechanism of toxicity is a hypersensitivity reaction to allopurinol or its major metabolite, oxipurinol, leading to immune complex deposition and diffuse vasculitis. Almost all organs have been involved. The accumulation of oxipurinol correlates with the development of the syndrome. Because oxipurinol clearance is directly related to renal function, allopurinol hypersensitivity is closely associated with renal insufficiency.[7] Although the half-life of oxipurinol is about 20 hours in patients with normal renal function, it is 250 hours when a patient has anuria.[8] This long half-life explains why our patient still had an oxipurinol level of 61 μmol per liter 14 days after her last dose. We note that earlier serum specimens were unavailable for assay. Other risk factors in addition to the reduced renal function for the development of the sensitivity syndrome include advanced tophaceous gout, chronic alcoholism, and severe liver disease.[9]

No effective treatment exists. Steroid therapy has been advocated by some,[10] although the sum of the data does not suggest a beneficial effect.[11] Oxipurinol can be removed from the body fluids by dialysis, and this has occasionally been beneficial.[12] As our patient was concomitantly started on hemodialysis, it is difficult to comment on the benefits of steroids, although some benefit seems to have been derived when the rash recurred and a more gradual taper was attempted.

Clearly early recognition of the syndrome, withdrawal of the drug, and supportive care remain the mainstay of therapy. In a patient for whom allopurinol therapy is clearly indicated, the dosage must be adjusted for renal function because this appears to be a major risk factor for the development of this syndrome. The importance of an approved indication cannot be overemphasized, given the fact that in more than half of the cases in the literature, treatment was being given for asymptomatic hyperuricemia.

REFERENCES

1. DeSwarte RD: Drug allergy—Problems and strategies. J Allergy Clin Immunol 1984; 74:209-224

2. Arellano F, Sacristán JA: Allopurinol hypersensitivity syndrome: A review. Ann Pharmacother 1993; 27:337-343

3. Auböck J, Fritsch P: Asymptomatic hyperuricaemia and allopurinol induced toxic epidermal necrolysis. Br Med J [Clin Res] 1985; 290:1969-1970

4. Singer JZ, Wallace SL: The allopurinol hypersensitivity syndrome. Arthritis Rheum 1986; 29:82-87

5. Lupton GP, Odom RB: The allopurinol hypersensitivity syndrome. J Am Acad Dermatol 1979; 1:365-374

6. Young JL Jr, Boswell RB, Nies AS: Severe allopurinol hypersensitivity—Association with thiazides and prior renal compromise. Arch Intern Med 1974; 134:553-558

7. Cacas EP: The allopurinol hypersensitivity syndrome: Its relationship to plasma oxypurinol levels. Adv Exp Med Biol 1989; 253A:257-260

8. Hande KR, Noone RM, Stone WJ: Severe allopurinol toxicity—Descriptions and guidelines for prevention in patients with renal insufficiency. Am J Med 1984; 176:47-56

9. Rundles RW: The development of allopurinol. Arch Intern Med 1985; 145:1492-1503

10. Lang PG Jr: Severe hypersensitivity reactions to allopurinol. South Med J 1979; 72:1361-1368

11. Al-Kawas FH, Seeff LB, Berendson RA, Zimmerman HJ, Ishak KG: Allopurinol hepatotoxicity—Report of two cases and review of the literature. Ann Intern Med 1981; 95:588-590

12. Elion GB, Benera FM, Beardmore TD, et al: Studies with allopurinol in patients with impaired renal function, *In* Rapado A, Watts RWE, DeBrurn CHMM (Eds): Purine Metabolism in Man: Clinical and Therapeutic Aspects. New York, NY, Plenum Press, 1979, pp 263-268